Targeting neuronal activity-regulated neuroligin-3 dependency in high-grade glioma.

Journal:	Nature
Publication Year:	2017
Authors:	Humsa S Venkatesh, Lydia T Tam, Pamelyn J Woo, James Lennon, Surya Nagaraja, Shawn M Gillespie, Jing Ni, Damien Y Duveau, Patrick J Morris, Jean J Zhao, Craig J Thomas, Michelle Monje
PubMed link:	28959975
Funding Grants:	Stem Cell Mechanisms Governing Discrete Waves of Gliogenesis in the Childhood Brain, White matter neuroregeneration after chemotherapy: stem cell therapy for "chemobrain"

Public Summary:

High-grade gliomas (HGG) are a devastating group of cancers, and represent the leading cause of brain tumour-related death in both children and adults. Therapies aimed at mechanisms intrinsic to glioma cells have translated to only limited success; effective therapeutic strategies will need also to target elements of the tumour microenvironment that promote glioma progression. Neuronal activity promotes the growth of a range of molecularly and clinically distinct HGG types, including adult and paediatric glioblastoma (GBM), anaplastic oligodendroglioma, and diffuse intrinsic pontine glioma (DIPG). An important mechanism that mediates this neural regulation of brain cancer is activity-dependent cleavage and secretion of the synaptic adhesion molecule neuroligin-3 (NLGN3), which promotes glioma proliferation through the PI3K-mTOR pathway. However, the necessity of NLGN3 for glioma growth, the proteolytic mechanism of NLGN3 secretion, and the further molecular consequences of NLGN3 secretion in glioma cells remain unknown. Here we show that HGG growth depends on microenvironmental NLGN3, identify signalling cascades downstream of NLGN3 binding in glioma, and determine a therapeutically targetable mechanism of secretion. Patient-derived orthotopic xenografts of paediatric GBM, DIPG and adult GBM fail to grow in Nlgn3 knockout mice. NLGN3 stimulates several oncogenic pathways, such as early focal adhesion kinase activation upstream of PI3K-mTOR, and induces transcriptional changes that include upregulation of several synapse-related genes in glioma cells. NLGN3 is cleaved from both neurons and oligodendrocyte precursor cells via the ADAM10 sheddase. ADAM10 inhibitors prevent the release of NLGN3 into the tumour microenvironment and robustly block HGG xenograft growth. This work defines a promising strategy for targeting NLGN3 secretion, which could prove transformative for HGG therapy.

Scientific Abstract:

High-grade gliomas (HGG) are a devastating group of cancers, and represent the leading cause of brain tumour-related death in both children and adults. Therapies aimed at mechanisms intrinsic to glioma cells have translated to only limited success; effective therapeutic strategies will need also to target elements of the tumour microenvironment that promote glioma progression. Neuronal activity promotes the growth of a range of molecularly and clinically distinct HGG types, including adult and paediatric glioblastoma (GBM), anaplastic oligodendroglioma, and diffuse intrinsic pontine glioma (DIPG). An important mechanism that mediates this neural regulation of brain cancer is activity-dependent cleavage and secretion of the synaptic adhesion molecule neuroligin-3 (NLGN3), which promotes glioma proliferation through the PI3K-mTOR pathway. However, the necessity of NLGN3 for glioma growth, the proteolytic mechanism of NLGN3 secretion, and the further molecular consequences of NLGN3 secretion in glioma cells remain unknown. Here we show that HGG growth depends on microenvironmental NLGN3, identify signalling cascades downstream of NLGN3 binding in glioma, and determine a therapeutically targetable mechanism of secretion. Patient-derived orthotopic xenografts of paediatric GBM, DIPG and adult GBM fail to grow in Nlgn3 knockout mice. NLGN3 stimulates several oncogenic pathways, such as early focal adhesion kinase activation upstream of PI3K-mTOR, and induces transcriptional changes that include upregulation of several synapse-related genes in glioma cells. NLGN3 is cleaved from both neurons and oligodendrocyte precursor cells via the ADAM10 sheddase. ADAM10 inhibitors prevent the release of NLGN3 into the tumour microenvironment and robustly block HGG xenograft growth. This work defines a promising strategy for targeting NLGN3 secretion, which could prove transformative for HGG therapy.

Source URL: https://www.cirm.ca.gov/about-cirm/publications/targeting-neuronal-activity-regulated-neuroligin-3-dependency-high-

grade